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(71) Applicants *(for all designated States except US)*: CSL LIMITED [AU/AU]; 45 Poplar Road, Parkville, VIC 3052 (AU). THE UNIVERSITY OF NEW SOUTH WALES [AU/AU]; Anzac Parade, Kensington, NSW 2033 (AU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: DOIDGE, Christopher, Vincent [AU/AU]; 72 Margaret Street, Box Hill, VIC 3128 (AU). LEE, Adrian [AU/AU]; 68 Austin Street, Lane Cove, NSW 2066 (AU).

(74) Agents: SLATTERY, John, Michael et al.; Davies Collison Cave, 1 Little Collins Street, Melbourne, VIC 3000 (AU).

(54) Title: TREATMENT OF *H. PYLORI* ASSOCIATED GASTRODUODENAL DISEASE

(57) Abstract

A method for the treatment of *Helicobacter* infection, preferably *H. pylori* infection in a mammalian host such as a human comprises administration to the infected host of an immunologically effective amount of one or more *Helicobacter* antigen(s), preferably in association with a mucosal adjuvant such as cholera toxin or *E.coli* heat labile toxin.

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TREATMENT OF *H. PYLORI* ASSOCIATED GASTRODUODENAL DISEASE

FIELD OF THE INVENTION

This invention relates to the treatment of gastroduodenal disease associated with *Helicobacter pylori* infection and in particular it relates to the use of active immunisation as a treatment for *H. pylori* -associated gastroduodenal disease.

BACKGROUND OF THE INVENTION

The bacterium, *Helicobacter pylori* , is now well established as a major gastroduodenal pathogen, and more than 50% of the world population is infected with this organism which causes gastritis of varying severity. While no symptoms are apparent in a great proportion of infected persons, in a significant number of *H. pylori* infected persons overt disease may result. The majority (95%) of duodenal ulcers are associated with *H. pylori* infection; a causal role is shown by treatment studies which indicate that if the organisms can be eradicated at the time of ulcer healing then the ulcers do not recur - in contrast to 80% recurrence rate at one year in those who remain infected with the organisms. Furthermore, up to 80% of gastric ulcers are thought to be *H. pylori* associated (Blaser, 1992).

There is now increasing evidence of the harmful consequence of long term *H. pylori* infection. In countries such as China, Colombia and Japan the bacterium is picked up very early in life, and in these persons the gastritis slowly progresses until after 30-40 years of continual infection, severe gastric atrophy appears. Gastric atrophy is well documented as being the precursor lesion for gastric cancer, although the actual cancer that develops in an atrophied stomach is dependent on a myriad of other factors including diet. However, all the evidence to date would suggest that the cancer would not develop if it was

possible to remov the *H. pylori* infection at an early age before the atrophy had developed (Parsonn t *et al.* , 1991).

There is no laboratory animal model of *H. pylori* infection that can be used for large scale assessment of new anti-*H. pylori* therapies. However, a *Helicobacter felis* mouse model of gastric *Helicobacter* infection has been developed that has proved extremely useful in the screening of the potential of new antimicrobial therapeutic regimens. *H. felis* is a spiral shaped bacterium that is very closely related to *H. pylori* . This bacterium colonises the stomach of mice in a very similar way to *H. pylori* in the human, i.e. the main ecological niche is gastric mucus and the localisation of colonisation is antral dominant. In germfree mice, *H. felis* infection induces a gastritis that is very similar to the human *H. pylori* infection with a chronic inflammation accompanied by polymorphonuclear leucocyte infiltration. Infection with each organism results in the induction of a similar raised immune response against *H. pylori* and *H. felis* respectively (Lee *et al.* , 1990).

The *H. felis* mouse model has proved to be very predictive of the efficacy of anti-*H. pylori* agents in humans. Thus, monotherapy with agents with high *in vitro* activity such as erythromycin show no significant *in vivo* effect against *H. felis* in mice, just as erythromycin has no anti-*H. pylori* effect in humans despite high antimicrobial effects *in vitro*. In contrast, the triple therapy regimens of a bismuth compound, metronidazole, and tetracycline or amoxycillin lead to a very high eradication rate in *H. felis* infected mice (Dick-Hegedus and Lee, 1991). Such triple therapies are the most successful human anti-*H. pylori* regimens, and at the present time are recommended as the first choice for anti-*H. pylori* therapy. However, established *Helicobacter* infections are difficult to treat, and current chemotherapeutic regimens remain suboptimal due to problems with efficacy, toxicity, drug resistance and reinfection (O'Connor, 1992).

Active immunisation of already infected patients has not been proven efficacious for any clinically manifest human infectious disease (Burke, 1992).

Given that *H. pylori* infections persist for long periods, if not the life of the infected individual, despite the presence of a vigorous immune response that includes a high level of circulating IgG antibody in the serum and the demonstration of local specific IgA antibody in the gastric mucosa, it has been considered that active immunisation was unlikely to be effective in therapy (Goodwin, 1993). Indeed, Czinn *et al.* (1993) in proposing that oral vaccination may be a feasible approach for the prevention of *H. pylori* infection in humans (based on an evaluation of an oral immunisation protocol in the *H. felis* mouse model), suggested that once infection is established neither antibody nor antibiotics are very effective at eradication.

Varga *et al.* (1992) have reported that a *H. pylori* vaccine prepared from organisms derived from a patient, and injected parenterally into that patient, resulted in an allergic reaction and failure to eradicate the organism.

Surprisingly, it has now been discovered for the first time that there is indeed a therapeutic potential for active immunisation against gastric *Helicobacter* infection. Furthermore, it has been discovered that oral administration of *H. pylori* antigen, with a suitable mucosal adjuvant, does not result in allergic or hypersensitivity symptoms, but results in suppression or eradication of the infecting organisms from the gastric mucosa.

SUMMARY OF THE INVENTION

According to one aspect of the present invention, there is provided a method for the treatment of *Helicobacter* infection in a mammalian host, which comprises the oral administration to said infected host of an immunologically effective amount of one or more *Helicobacter* antigen(s), optionally in association with a mucosal adjuvant.

In another aspect, there is provided a vaccine composition for the treatment of *Helicobacter* infection in a mammalian host, which comprises an

immunologically effective amount of one or more *Helicobacter* antig n(s), optionally in association with a mucosal adjuvant.

In yet another aspect, the present invention provides the use of a vaccine composition comprising an immunologically effective amount of one or more *Helicobacter* antigen(s), optionally in association with a mucosal adjuvant, in the treatment of *Helicobacter* infection in a mammalian host.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

By use of the term "immunologically effective amount" herein, it is meant that the administration of that amount to an individual infected host, either in a single dose or as part of a series, is effective for treatment of *Helicobacter* infection. This amount varies depending upon the health and physical condition of the individual to be treated, the taxonomic group of individual to be treated, the capacity of the individual's immune system to synthesise antibodies, the degree of protection desired, the formulation of the vaccine, the assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

DETAILED DESCRIPTION OF THE INVENTION

The *Helicobacter* antigen(s) used in accordance with the present invention may be *H. felis* antigen(s), or more preferably *H. pylori* antigen(s). In a particularly preferred aspect of the present invention, a vaccine composition comprising *H. pylori* antigen(s) in association with a mucosal adjuvant is used in the treatment of *H. pylori* infection in a human patient.

Preferably, the *Helicobacter* antigen(s) comprise a bacterial sonicate, and in particular a *H. pylori* sonicate. More preferably, the *Helicobacter* antigen(s) used in accordance with the present invention comprise inactivated whole bacterial cells of *H. pylori* .

Alternatively, the *Helicobacter* antigen(s) used in accordance with the present invention may comprise one or more individual antigens, particularly one or more *H. pylori* antigens such as *H. pylori* urease, or *H. pylori* cytotoxin (CT), Cytotoxin Associated Immunodominant (CAI) antigen or heat shock protein (hsp) as disclosed by way of example in International Patent Publication No. WO 93/18150.

One mucosal adjuvant which is optionally, and preferably, administered with the *Helicobacter* antigen(s) to the infected host is cholera toxin. Another preferred mucosal adjuvant which may be administered with the *Helicobacter* antigen(s) is *E.coli* heat labile toxin (*E.coli* HLT). Mucosal adjuvants other than cholera toxin and *E.coli* HLT which may be used in accordance with the present invention include non-toxic derivatives of cholera toxin, such as the B sub-unit (CTB), chemically modified cholera toxin, or related proteins produced by modification of the cholera toxin amino acid sequence. Each of these molecules with mucosal adjuvant or delivery properties may be added to, or conjugated with, the *Helicobacter* antigen(s). Other compounds with mucosal adjuvant or delivery activity may be used, such as: bile; polycations such as DEAE-dextran and polyornithine; detergents such as sodium dodecyl benzene sulphate; lipid-conjugated materials; antibiotics such as streptomycin; vitamin A; and other compounds that alter the structural or functional integrity of mucosal surfaces. Other mucosally active compounds include derivatives of microbial structures such as MDP; acridine and cimetidine.

Helicobacter antigen(s) may be delivered in accordance with this invention in ISCOMS (immun stimulating complexes), ISCOMS containing CTB, liposomes or encapsulated in compounds such as acrylates or poly(DL-lactide-co-glycoside)

to form microspheres of a size suit d to adsorption by M cells. Alternatively, micro or nanoparticles may be covalently attached to molecules such as vitamin B12 which have specific gut receptors. Antigen(s) may also be incorporated into oily emulsions and delivered orally. An extensive though not exhaustive list of adjuvants can be found in Cox and Coulter, 1992.

Other adjuvants, as well as conventional pharmaceutically acceptable carriers, excipients, buffers or diluents, may also be included in the therapeutic vaccine composition of this invention. The vaccine composition may, for example, be formulated in enteric coated gelatine capsules including sodium bicarbonate buffers together with the *Helicobacter* antigen(s) and mucosal adjuvant.

Generally, a vaccine composition in accordance with the present invention will comprise an immunologically effective amount of *Helicobacter* antigen(s), and optionally a mucosal adjuvant, in conjunction with one or more conventional pharmaceutically acceptable carriers and/or diluents. As used herein "pharmaceutically acceptable carriers and/or diluents" include any and all solvents, dispersion media, aqueous solutions, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art and is described by way of example in *Remington's Pharmaceutical Sciences*, 18th Edition, 1990, Mack Publishing Company, Pennsylvania, U.S.A..

The pharmaceutical composition of this invention may be orally administered directly to the mammalian host, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatine capsule, or it may be compressed into tablets, or it may be incorporated directly with the solid or liquid food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestibl tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentag of active component

in the compositions and preparations may of course be varied and is such that a suitable dosage will b obtained to be immunologically effective.

Solid oral dosage units such as tablets, troches, pills, capsules and the like may also contain the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavouring agent such as peppermint, oil of wintergreen, or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active component, sucrose as a sweetening agent, methyl and prophylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed.

The vaccine composition of the invention is administered orally in amounts readily determined by persons of ordinary skill in this art. Thus, for adults a suitable dosage would be in the range of 10 μg to 10 g, for example 50 μg to 3g. Similar dosage ranges would be applicable for children.

As noted above, a suitable mucosal adjuvant is cholera toxin. The amount of mucosal adjuvant employed depends on the type of mucosal adjuvant used. For example, when the mucosal adjuvant is cholera toxin, it is suitably used in an amount of 10 nanogram to 50 μg, for example 01 μg to 10 μg. When the mucosal adjuvant is *E.coli* heat labile toxin, suitable amounts are 1 μg to 1 mg, for example 5 μg to 50 μg.

In w rk leading to the present invention, active immunisation of mice previously infected with *H. felis* , with oral doses of cholera toxin or *E.coli* HLT adjuvant and a whole cell *H. felis* or *H. pylori* sonicate, result in the clearance of *H. felis* from the gastric mucosa. It is therefore anticipated that active immunisation of infected humans with oral doses of a mucosal adjuvant with *H. pylori* antigen(s) will result in the clearance of *H. pylori* from the gastric mucosa. Based on previous studies with this model using anti-*H. pylori* agents, it is considered that this is the first evidence of the therapeutic potential of active immunisation with *H. pylori* vaccines, and indicates that a vaccine composition for the therapy of human *H. pylori* -associated gastroduodenal disease is a preparation of *Helicobacter* antigen(s), optionally and preferably combined with a mucosal adjuvant.

It will be apparent to persons skilled in the field that effective treatment of *Helicobacter pylori* infection in humans with an oral vaccine composition of *Helicobacter* antigen(s) which will eradicate or suppress the infection will provide a significant therapeutic benefit via the suppression or elimination of gastritis, prevention of peptic ulcer relapse and reduction in the harmful sequelae of *Helicobacter pylori* infection including peptic ulceration and gastric cancer.

The present invention is further illustrated in the following, non-limiting Examples.

EXAMPLE 1

One hundred and sixty female SPF mice from the Animal Breeding Unit of the University of New South Wales, Australia, were infected with four oral doses of 10^9-10^{10} living *Helicobacter felis* (ATCC culture 49179) given two days apart.

Bacteria were grown in plastic Petri dishes on Blood Agar Base No.2, 3.8% w/v (Oxoid, Basingstoke, U.K.) with 7% v/v whole horse blood (Oxoid), containing amphotericin B (Fungizone, Squibb, Princeton, N.J., USA) 2.5 mg/l; trimethoprim

(Sigma, St.Louis, MO, USA), 10 mg/l. Plates wer incubated in a microaerophilic humid atmosphere (Oxoid, BR56) at 37°C for 48 hours.

Sonicates were prepared by growth of the organisms, as described above, followed by harvesting of the organisms in 0.1 molar phosphate buffered saline (PBS). The cells were washed, collected by centrifugation, washed once in PBS, and resuspended in fresh PBS. The cells were then sonicated at the rate of one minute per ml of cell suspension (50% duty cycle) using a B-30 Branson Cell Disrupter. The sonicate was stored at -20°C.

On days 28, 42, 44 and 47 after administration of the last infecting dose of *H. felis* , 20 of the mice were given orally 0.2 ml of a suspension containing 10 μg of cholera toxin (Sigma C 3012) and a sonicate of *H. felis* containing 1 mg protein (BIO-RAD DC protein assay).

Samples of antral mucosa were tested for infection using a rapid microtitre urease test as described previously (Lee *et al.* , 1990). This test has been validated as being highly predictive of *H. felis* gastric infection. Groups of 40 mice (20 vaccinates and 20 controls) were euthanased at intervals of 1 week, 1 month, 2 months and 3 months after the last dose of vaccine.

The results are shown in Table 1.

These results show that treatment of *H.felis* infected mice with an oral vaccine comprised of Helicobacter antigens and a mucosal adjuvant, results in cure of the infection in a significant proportion of mice. This effect is evident 1 week after cessation of therapy, and continues for at least 3 months, demonstrating that the mice have been cured of their infection.

TABLE 1

Immunisation	Proportion of *H.felis* infected mice			
	1 week	1 month	2 months	3 months
Nil	19/19	20/20	18/19	13/19
Sonicate plus CT	2/20	3/20	6/20	1/17
	P<0.0001*	P<0.0001	P<0.05	P<0.0001

* Fisher's exact test (two tailed).

EXAMPLE 2

One hundred female BALB/c mice from the Animal Breeding Unit of the University of New South Wales, Australia, were infected with 3 oral doses of 10^8 living *Helicobacter felis* (ATCC culture 49179) given 2 days apart, i.e. days 1, 3 and 5.

Bacteria were grown in plastic Petri dishes on Blood Agar Base No. 2, 3.8% w/v (Oxoid, Basingstoke, U.K.) with 7% v/v whole horse blood), (Oxoid), containing amphotericin B (Fungizone, Squibb, Princeton, N.J., USA) 2.5 mg/l; trimethoprim (Sigma, St.Louis, MO, USA), 10 mg/l. Plates were incubated in a microaerophilic humid atmosphere (Oxoid, BR56) at 37°C for 48 hours.

Sonicates were prepared by growth of the organisms, as described above, followed by harvesting of the organisms in 0.1 molar phosphate buffered saline (PBS). The cells were washed collected by centrifugation, washed once in PBS, and resuspended in fresh PBS. The cells were then sonicated at the rate of one per minute per ml of cell suspension (50% duty cycle) using a B-30 Branson Cell Disrupter. The sonicate was stored at -20°C.

On days 21, 35, 37, and 40 after administration of the last infecting dose of *H. felis*, 20 mice were each given orally 0.2 ml of a solution containing 10 ug of cholera toxin (Sigma C 3012), 20 mice were each given orally 0.2 ml of a suspension containing 10 ug of cholera toxin and a sonicate of *H. felis* containing 1 mg protein (BIO-RAD DC protein assay), 20 mice were each given orally 0.2 ml of a suspension containing a sonicate of *H. felis* containing 1 mg protein, 20 mice were each given orally 0.2 ml of a suspension containing 10 ug of cholera toxin and a sonicate of *H.pylori* (strain 921023) containing 1 mg protein, and 20 mice were not orally vaccinated.

One week after the final immunising dose all the mice were euthanased. Samples of antral mucosa were tested for infection using a rapid microtitre urease test as described previously (Lee *et al.*, 1990). This test has been validated as being highly predictive of *H. felis* gastric infection.

The results are shown in Table 2.

These results show that oral administration of Helicobacter antigens derived from either *H. felis*, or *H. pylori* along with a mucosal adjuvant, will cure a significant portion of *H. felis* infected mice.

TABLE 2

Vaccine	Number of animals infected	Significance
Nil	16/20	
CT alone	15/20	N.S.
H. felis sonicate alone	12/20	N.S.
H. felis sonicate plus CT	8/19	P<0.05*
H. pylori sonicate plus CT	4/20	P<0.001

* Fisher's xact test (two tailed)

EXAMPLE 3

One hundred female SPF mice from the Animal Breeding Unit of the University of New South Wales, Australia, were infected with 4 oral doses of 10^9-10^{10} living *Helicobacter felis* (ATCC culture 49179) given 2 days apart. 20 female SPF mice were left uninfected, as negative controls.

Bacteria were grown in plastic Petri dishes on Blood Agar Base No. 2, 3.8% w/v (Oxoid, Basingstoke, UK) with 7% v/v whole horse blood (Oxoid), containing amphotericin B (Fungizone, Squibb, Princeton, N.J., USA) 2.5 mg/l; trimethoprim (Sigma, St.Louis, MO, USA), 10 mg/l. Plates were incubated in a microaerophilic humid atmosphere (Oxoid, BR56) at 37°C for 48 hours.

Sonicates were prepared by growth of the organisms, as described above, followed by harvesting of the organisms in 0.1 molar phosphate buffered saline (PBS). The cells were washed, collected by centrifugation, washed once in PBS, and resuspended in fresh PBS. The cells were then sonicated at the rate of one per minute per ml of cell suspension (50% duty cycle) using a B-30 Branson Cell Disrupter. The sonicate was stored at -20°C.

Starting between 6 weeks and 9 weeks after their last infecting dose of *H. felis,* 20 mice were each given orally 0.2 ml of a solution containing 25 μg of *E.coli* heat labile toxin (HLT) (Sigma E 8015), 20 mice were each given orally 0.2 ml of a suspension containing 25 μg of HLT and a sonicate of *H. pylori* containing 1 mg protein (BIO-RAD DC protein assay), 20 mice were each given orally 0.2 ml of a suspension containing a sonicate of *H. pylori* containing 1 mg protein, and 40 mice were not orally vaccinated.

Each group received three further doses 15, 17 and 20 days after their initial dose.

Four weeks after the final immunising dose all th mic were uthanased. Samples of antral mucosa were tested for inf ction using a rapid microtitre urease test as described previously (Lee *et al.* , 1990). This test has been validated as being highly predictive of *H. felis* gastric infection.

The results are shown in Table 3.

They show that oral administration of *Helicobacter* antigens derived from *H. pylori* along with a mucosal adjuvant *E.coli* heat labile toxin, will cure a significant portion of *H. felis* infected mice.

TABLE 3

Treatment Group	Proportion of *H. felis* infected mice.
Uninfected, unvaccinated	0/20
Infected, unvaccinated	40/40
Infected, Hp antigen alone	20/20
Infected, *E.coli* HLT alone	20/20
Infected, Hp antigen & HLT	6/19*

* P<0.0001 (Fisher's exact test, two tailed).

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CLAIMS.

1. A method for the treatment of *Helicobacter* infection in a mammalian host, which comprises the oral administration to said infected host of an immunologically effective amount of one or more *Helicobacter* antigen(s), optionally in association with a mucosal adjuvant.

2. A method according to claim 1, wherein said *Helicobacter* antigen is *H. pylori* antigen.

3. A method according to claim 1, wherein said *Helicobacter* antigen is *H. felis* antigen.

4. A method according to claim 1, wherein said *Helicobacter* antigen(s) comprises a sonicate of *Helicobacter* cells, preferably *H. pylori* cells.

5. A method according to claim 1, wherein said *Helicobacter* antigen is administered in association with a mucosal adjuvant.

6. A method according to claim 5, wherein said mucosal adjuvant is cholera toxin or *E.coli* heat labile toxin.

7. A method according to claim 1, wherein said infected host is an infected human.

8. A vaccine composition for the treatment of *Helicobacter* infection in a mammalian host comprising an immunogenically effective amount of one or more *Helicobacter* antigen(s), optionally in association with a mucosal adjuvant, together with a pharmaceutically acceptable carrier or diluent.

9. A vaccine composition according to claim 8, further comprising an effective amount of a mucosal adjuvant.

10. A vaccine composition according to claim 8, wherein said mucosal adjuvant is cholera toxin or *E.coli* heat labile toxin.

11. A vaccine composition according to claim 8, wherein said *Helicobacter* antigen is *H. pylori* antigen.

12. A vaccine composition according to claim 8, wherein said *Helicobacter* antigen is *H. felis* antigen.

13. A vaccine composition according to claim 8, wherein said *Helicobacter* antigen(s) comprises a sonicate of *Helicobacter* cells, preferably *H. pylori* cells.

14. Use of a vaccine composition comprising an immunologically effective amount of one or more *Helicobacter* antigen(s), optionally in association with a mucosal adjuvant, in the treatment of *Helicobacter* infection in a mammalian host.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 94/00416

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.[6] A61K 39/02, 39/108

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl.[6] A61K 39/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)

CAS
DERWENT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	AU 55619/94 (FONDATION POUR LA RECHERCHE DES MALADIES GASTRO-INTESTINALES : GASTROFONDS MANDATRIA FIDUCIAIRE SA) 11 May 1994 (11.05.94)	1, 7, 10, 14
P,X	WO 93/20843 (CZINN S.J and NEDRUD J.G.) 28 October 1993 (28.10.93)	1, 7, 8, 14
P,X	WO 93/16723 (VANDERBILT UNIVERSITY) 2 September 1993 (02.09.93)	8, 11
X	DE 4139840 (QUIDEL CORP) 11 June 1992 (11.06.92)	8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/AU

AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION
PO BOX 200
WODEN ACT 2606
AUSTRALIA

Facsimile No. 06 2853929

Authorized officer

J.P. PULVIRENTI

Telephone No. (06) 2832253

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 94/00416

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
AU	55619/94	WO	9409823
WO	9320843	WO	9320843
WO	9316723	AU	37282/93
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END OF ANNEX